Advanced Drug Delivery Reviews 96 (2016) 161–175

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Biomechanical conditioning of tissue engineered heart valves: Too much of a good thing?☆

Shouka Parvin Nejad [a,b], Mark C. Blaser [a,b], J. Paul Santerre [a,b,c], Christopher A. Caldarone [a,b,d], Craig A. Simmons [a,b,c,e,*]

[a] The Ted Rogers Centre for Heart Research, 661 University Avenue, 14th Floor, Toronto, ON M5G 1M1, Canada
[b] Institute of Biomaterials & Biomedical Engineering, University of Toronto, 164 College Street, Toronto, ON M5S 3G9, Canada
[c] Faculty of Dentistry, University of Toronto, 124 Edward Street, Toronto, ON M5G 1G6, Canada
[d] Division of Cardiovascular Surgery, Department of Pediatrics, University of Toronto, Hospital for Sick Children, Toronto, ON M5G 1X8, Canada
[e] Department of Mechanical & Industrial Engineering, University of Toronto, 5 King's College Road, Toronto, ON M5S 3G8, Canada

ARTICLE INFO

Article history:
Received 7 September 2015
Received in revised form 23 October 2015
Accepted 2 November 2015
Available online 10 November 2015

Keywords:
Heart valves
Tissue engineering
Valvular interstitial cells
Mechanobiology
Fibrosis
Bioreactors
Mechanical conditioning
Mesenchymal stem cells

ABSTRACT

Surgical replacement of dysfunctional valves is the primary option for the treatment of valvular disease and congenital defects. Existing mechanical and bioprosthetic replacement valves are far from ideal, requiring concomitant anticoagulation therapy or having limited durability, thus necessitating further surgical intervention. Heart valve tissue engineering (HVTE) is a promising alternative to existing replacement options, with the potential to synthesize mechanically robust tissue capable of growth, repair, and remodeling. The clinical realization of a bioengineered valve relies on the appropriate combination of cells, biomaterials, and/or bioreactor conditioning. Biomechanical conditioning of valves in vitro promotes differentiation of progenitor cells to tissue-synthesizing myofibroblasts and prepares the construct to withstand the complex hemodynamic environment of the native valve. While this is a crucial step in most HVTE strategies, it also may contribute to fibrosis, the primary limitation of engineered valves, through sustained myofibrogenesis. In this review, we examine the progress of HVTE and the role of mechanical conditioning in the synthesis of mechanically robust tissue, and suggest approaches to achieve myofibroblast quiescence and prevent fibrosis.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Tissue engineering of the heart: from in vitro models to regenerative solutions".

* Corresponding author at: Institute of Biomaterials & Biomedical Engineering, University of Toronto, 164 College Street, Toronto, Ontario M5S 3G9, Canada.
E-mail address: c.simmons@utoronto.ca (C.A. Simmons).

http://dx.doi.org/10.1016/j.addr.2015.11.003
0169-409X/

1. Introduction

The global health, economic, and societal impact of heart valve disease is alarming. In the developing world, rheumatic valve disease causes 282,000 deaths annually, comparable to all cardiovascular disease-related deaths in the U.S. [1]. Over 300,000 heart valve replacement surgeries are performed annually worldwide [2]. In the U.S. alone, more than 100,000 heart valve surgeries were performed in 2006 at a cost of over $14 billion [3]. Strikingly, the number of patients requiring valve replacement worldwide will triple by 2050 [2], leading some to describe heart valve disease as “the next cardiac epidemic” [4].

There are no medical treatments for dysfunctional valves and the majority of diseased valves are not repairable [5], leaving surgical replacement as the primary treatment option. Dysfunctional valves are replaced with mechanical, bioprosthetic, or cryopreserved homograft valves. Replacement with these prostheses enhances survival and quality of life for many patients, but prosthetic valves are not without limitations. Mechanical valves are thrombogenic, requiring lifelong anticoagulation and the associated lifestyle restrictions [6], and are prone to infection that is difficult to eradicate [7]. Bioprosthetic valves, made from porcine or bovine tissue, have poor durability owing to rapid leaflet mineralization and mechanical tearing, a phenomenon that is more pronounced in younger, more physically and metabolically active patients [8]. Cryopreserved homografts suffer the same structural degradation problems as bioprosthetic valves and are in limited supply [9]. Importantly, no current prosthetic valve has the capacity for growth, repair, and adaptation, features that are essential for pediatric patients with congenital defects, children and young adult rheumatic fever patients, and active adult patients with valve disease.

Heart valve tissue engineering (HVTE) may address this unmet need, particularly for pediatric patients who would benefit the most from a living replacement valve. However, despite much progress over the past two decades, the promise of HVTE has yet to be realized clinically. Significant advances towards clinical utility will likely come from improved understanding of native valve biology and translation of that knowledge to guide regenerative strategies and the design of tissue engineered replacements. Here we review aspects of native valve (patho) biology relevant to HVTE and the progression of valve regeneration strategies. We complement recent reviews on the biomaterial [10], biological [11], manufacturing [12], and translational [13] aspects of HVTE by focusing on the critical role that biomechanical stimuli play in regulating native valve (patho)biology and the beneficial and potentially detrimental implications for HVTE.

2. Native valve function and physiology

The human heart has four valves that ensure one-way flow of blood through the chambers of the heart. The valves between the atria and ventricles (mitral valve on the left side of the heart; tricuspid valve on the right) are classified structurally and anatomically as atrioventricular valves, while the semilunar valves sit between the ventricles and arteries leaving the heart (aortic valve on the left; pulmonary valve on the right).

The semilunar valves are the most commonly affected by congenital abnormalities in children (often the pulmonary) and by disease in adults (primarily the aortic), and therefore are the principal targets for replacement with engineered tissue. The aortic and pulmonary valves are both composed of three thin, flexible cusps that contact during diastole to form coaptations that prevent retrograde blood flow back into the ventricles. Under systolic pressure, the valves open fully so as not to impede flow from the ventricles to the pulmonic and systemic circulations. With each cardiac cycle, the valve cusps undergo large deformations and are subjected to large shear stresses from flowing blood that put extreme mechanical demands on the cusp tissue, particularly for the aortic valve (reviewed in [14]). Remarkably, despite the cusps being only ~0.5 mm (pulmonary) [15] to 1 mm (aortic) [16] thick, they remain structurally intact and functional in most people for their lifetime. This feat is made possible by the elaborate structure of the cusp extracellular matrix (ECM) and by the resident cells, which repair and remodel the tissue in response to damage and varying cardiac function demands.

2.1. Semilunar valve cusp structure and function

The cusps of both the aortic and pulmonary valves are stratified into three distinct layers of ECM: the fibrosa, spongiosa, and ventricularis (Fig. 1). The fibrosa layer sits on the outflow side of the cusp, closest to the ascending aorta (for the aortic valve) or pulmonary artery (for the pulmonary valve). This layer is made up of high tensile strength, circumferentially-aligned type I and III collagen [17,18]. The middle layer is the spongiosa, which consists of glycosaminoglycans (GAGs), proteoglycans, and an interwoven mesh of fine elastin fibers [19]. GAGs and proteoglycans retain a large amount of water, and the spongiosa is thus able to resist compressive forces during valve opening and closing while also facilitating the large shape changes that the cusps undergo during the cardiac cycle [8,20]. Lastly, the ventricularis layer sits on the side of the cusp facing into the left or right ventricle, for the aortic and pulmonary valve respectively, and is composed of collagen and radially-aligned elastin [21]. The architecture of collagen and elastin fibers in the fibrosa and ventricularis layers confers greater tissue compliance in the radial than circumferential direction. For example, adult pulmonary valve leaflets from 20 to 50 year-old donors had uniaxial tensile elastic moduli of 1.32 MPa and 16 MPa at a stress level of 1.0 MPa in the radial and circumferential directions, respectively [22]. Notably, aortic valve leaflets from the same cohort had nearly identical radial (1.98 MPa) and circumferential moduli (15.3 MPa) [22]. The high degree of similarity in pulmonary and aortic valve structure, composition, and mechanical behavior implies that a common tissue engineering strategy and set of design criteria can be applied for adult aortic and pulmonary valves. It is not known if the same is true for pediatric valves. The specialized architecture of leaflet ECM fibers and the resulting anisotropic tissue mechanical properties are essential to the